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(54) METHOD OF MANUFACTURING OBJECTS DESIGNED FOR REPEATED OR LONG TERM CONTACT WITH LIVE TISSUES

(71) We, CESKOSLOVENSKA AKADEMIE VED, a Czechoslovakian Corporation of No. 3 Narodni, Praha 1, Czechoslovakia, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to a method of manufacturing objects designed for repeated or long-term contact with live tissues and mucous membranes, by polymerizing N-lower alkyl or N-lower hydroxyalkyl methacrylamides, if desired with a minor amount of one or more mono-olefinically unsaturated co-monomers, and with small amounts of a cross-linking monomer in the presence of water or a water-miscible liquid.

As is well known, non-ionic hydrogels based on sparingly cross-linked polymers of glycol monomethacrylates or glycol monoacrylates have heretofore been used for manufacturing contact lenses, prostheses for various somatic organs, implants, coatings of probes, catheters, drain tubes, cannulae, or the like, which materials are supposed to provide above all a good physiological compatibility and not to irritate living organisms. As it has been expected and also proved by laboratory tests on animals, analogous hydrogels comprising basic groups tend to irritate live tissues and are badly accepted by the host body, or in some cases healing of the tissues takes place tending to stick the article in position.

According to the invention we provide a method of manufacturing articles designed for repeated or long term contact with live tissue and mucous membranes, comprising copolymerizing in a mould a monomer mixture containing more than 50 mol. percent of a hydrophilic monomer selected from an N-lower alkyl (as herein defined) methacrylamide and N-lower hydroxyalkyl (as herein defined) methacrylamide, and from 0.1 to 2 mol. percent of a cross-linking compound having at least two polymerizable double bonds in its molecule, the copolymerization being initiated by a free-radical polymerization catalyst or UV radiation and being carried out in the presence of water or a water-miscible liquid in a quantity such that the resulting copolymer takes on the shape of the mould, said cross-linking compound being soluble in the monomer mixture. Long-term laboratory tests carried out on a large number of rats have proved that tissue irritations, if any, are limited to several days after the implantation of hydrogel whereupon they will disappear. Similarly as with other hydrogels and plastics in general, these materials get encapsulated by collagenous connective tissues but the encapsulating layer is sufficiently thin so as not to prevent both conventional surgical and prosthetic operations.

The monomer mixture may additonally include a mono-olefinically unsaturated monomer copolymerisable with said hydrophilic monomer. An advantage of both polymers and copolymers of N-alkyl methacrylamides resides in their considerable reresistance to hydrolytic agents and enzymes.

As the mono-olefinically unsaturated monomer copolymerisable with the hydrophilic monomer, are suitable, for instance, methacrylonitrile, acrylonitrile, methacrylamide, acrylamide, substituted acrylamides such as N-alkyl-acrylamides, and glycol mono-methacrylates derived from various glycols, such as ethylene glycol, di-ethylene glycol, tri-ethylene glycol, propylene glycol or butylene glycol. By appropriately choosing the composition of the monomer mixture it is possible to prepare a broad range of hydrophilic polymers, i.e. from sparingly cross-linked and highly swellable polymers of vitreous body types up to poorly water

swellable polymers. The hydrogels produced according to the present invention contain in equilibrious swollen state from 5 to 95 percent by weight of water calculated on the polymer weight.

The terms "lower alkyl" and "lower hydroxyalkyl", as used herein, mean, respectively, alkyl and hydroxyalkyl groups with 1 to 6 carbon atoms, with straight or branched chains. Water-miscible liquids that can be used are e.g. glycols, formamide and lower aliphatic alcohols.

The following examples are given as illustrative of the invention.

EXAMPLE I

An implant especially suitable as carrier for depositing an acidic medicament was prepared by polymerizing, in a suitable mould, a mixture of 79 percent of N-ethyl methacrylamide, one percent of diethylene glycol dimethacrylate, 0.02 percent of azo-bis-isobutyronitrile and water up to 100 percent. The mould was heated from the outside to 60° Centigrade. After 8 hours the polymerization was finished. The implant thoroughly washed was placed into a saline solution isotonic relative to the respective live tissue and comprising an appropriate medicament.

EXAMPLE II

A similar implant as described in Example 1 was prepared from a 70 percent aqueous solution of N-gamma-hydroxypropyl methacrylamide containing one percent of N,N-methylene-bis-methacrylamide and 0.05 percent of hydrogen peroxide. The polymerization was achieved within 8 hours heating the solution to 60° Centigrade in a mould.

EXAMPLE III

In a glass mould consisting of two ground plates spaced from each other by a distancing border layer, there was polymerized a 70 percent solution of N-hydroxy-n-butyl methacrylamide in n-butanol, comprising as cross-linking agent 0.3 percent of triethylene glycol dimethacrylate, and 0.02 percent of methyl azo-bis-isobutyrate. The polymerization was finished after 8 hours heating at 60° Centigrade. The thus formed foil washed in water and immersed in sterile physiological saline solution containing 350 p.p.m. of oxytetracycline hydrochloride was suitable as a temporary skin substitute after an accident.

EXAMPLE IV

In a glass mould as employed for manufacturing mammal prostheses there was heated a 70 percent aqueous solution of N-gamma-hydroxypropyl methacrylamide and N-propyl methacrylamide (2:1 ratio by weight), containing 0.5 percent of N,N-methylene-bis-methacrylamide and 3 percent of methyl azo-bis-isobutyrate, for a period of 4 hours to 80° Centigrade, the mould having been filled initially to half of its capacity. The thus obtained spongy prosthesis was several times centrifuged, washed again in physiological saline solution and finally immersed into physiological saline solution containing 50 p.p.m. of tetracycline hydrochloride.

EXAMPLE V

Into a glass mould consisting of two ground plates spaced by a distancing layer at their partition an open-mesh polyester knitwork was inserted. The mould was then filled up at room temperature with an 80 percent aqueous solution of N-methyl methacrylamide and ethylene glycol monomethacrylate (4:1 ratio), containing 0.4 percent of ethylene glycol-bis-methacrylate and 0.05 percent of di-isopropyl percarbonate. The solution was freed of air bubbles by evacuation and tapping whereupon it was polymerized by heating to 60° Centigrade for 6 hours. The thus formed hydrogel sheet was suitable, for example, as a peritoneum substitute, or the like.

EXAMPLE VI

Into a glass tube there was inserted seamless polyester knitwork and poured an 80 percent solution of a mixture of N-gamma-hydroxypropyl methacrylamide with methacrylonitrile (5:1 ratio) in n-butanol, containing one percent of methylene-bis-acrylamide and 0.05 percent of di-isopropyl percarbonate. The tube was closed at both ends to serve as a mould and was set into rapid rotation about its longitudinal axis, its temperature having been maintained by means of an infra red radiator at 70° Centigrade. The polymerization finished, the tube was flushed with luke warm water till the butanol was removed whereupon the reinforced hydrogel polymerisate was withdrawn. The product was suitable, for instance, as an arterial prosthesis.

EXAMPLE VII

Elastic bodies designed to fill up post-operation cavities were manufactured by heating, in a mould, a 70 percent solution of a mixture of N-propyl methacrylamide with acrylamide (3:1 ratio), containing 0.5 percent of N,N-methylene-bis-methacrylamide and 0.05 percent of azo-bis-butyronitrile in n-butanol, for several hours at 70° Centigrade. After the polymerization had been achieved the bodies were removed from the mould, washed in warm distilled water and finally immersed into physiological saline solution having an admixture of streptomycin and p-aminosalicylic acid in

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accordance with a physician's prescription.

All percentages referred to in the preceding Examples are to be understood by weight.

As hereinabove mentioned, the Examples are illustrative only and do not include all appropriate possibilities of mixed monomer compositions. The polymerisation can be promoted by means of various initiators which may be replaced by UV-irradiation, or if using special initiators capable of being decomposed into free radicals due to the absorption of rays within the visible spectrum band, the polymerization can be achieved by irradiation from a light source or by sun light. Likewise application or administration modes, i.e. types of objects designed for repeated or long-termed contact with live tissues or mucous membrane, are not limited to those disclosed in the above Examples. In this way it is also possible to prepare contraceptive intrauterine devices (CIUD), cosmetic prostheses, and the like.

WHAT WE CLAIM IS:—

1. A method of manufacturing articles designed for repeated or long term contact with live tissue and mucous membranes, comprising copolymerizing in a mould a monomer mixture containing more than 50 mol. percent of a hydrophilic monomer selected from an N-lower alkyl (as herein defined) methacrylamide and N-lower hydroxyalkyl (as herein defined) methacrylamide, and from 0.1 to 2 mol. percent of a cross-linking compound having at least two polymerizable double bonds in its molecule, the copolymerization being initiated by a free-radical polymerization catalyst or UV radiation and being carried out in the presence of water or a water-miscible liquid in a quantity such that the resulting copolymer takes on the shape of the mould, said cross-linking compound being soluble in the monomer mixture.

2. A method as claimed in claim 1, wherein the cross-linking compound having at least two polymerizable double bonds is N,N-methylene-bis-methacrylamide.

3. A method as claimed in claim 1 or claim 2, wherein the monomer mixture also contains a mono-olefinically unsaturated monomer copolymerizable with said hydrophilic monomer.

4. A method of manufacturing articles as described in any one of the examples described herein.

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